

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re Application of: Ke et al. )

Serial No.: 09/736,051 )

Group Art Unit: 1617

Filed: December 13, 2000 )

Examiner: Unassigned

For: COMBINATION THERAPY FOR  
OSTEOPOROSIS )

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Commissioner for Patents  
Washington, D.C. 20231

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Jean M. Marshall  
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*Jean M. Marshall*  
(Signature of person mailing paper)

Sir:

AMENDMENT UNDER 37 C.F.R. § 1.607

Prior to examination of the present application, please enter the following amendment.

IN THE CLAIMS:

Please cancel claims 31 and 32 without prejudice or disclaimer.

Please amend claims 34 and 36 as follows:

34. (Amended) A pharmaceutical composition comprising:

- a. a therapeutically effective amount of a first compound, said first compound being droloxifene, raloxifene, tamoxifen or idoxifene; and
- b. a therapeutically effective amount of a second compound, said second compound being sodium fluoride.

36. (Amended) A method for treating a mammal having a condition which presents with low bone mass comprising administering to a mammal having a condition which presents with low bone mass
- a. a therapeutically effective amount of a first compound, said first compound being droloxifene, raloxifene, tamoxifen or idoxifene; and
  - b. a therapeutically effective amount of a second compound, said second compound being sodium fluoride.

Please cancel claims 43 and 44 without prejudice or disclaimer.

Please amend claims 45 and 46 as follows:

45. (Amended) A kit containing a treatment for a condition which presents with low bone mass comprising:
- a. a therapeutically effective amount of droloxifene, raloxifene, tamoxifen or idoxifene and a pharmaceutically acceptable carrier in a first unit dosage form;
  - b. a therapeutically effective amount of a sodium fluoride and a pharmaceutically acceptable carrier in a second unit dosage form; and
  - c. container means for containing said first and second dosage forms.
46. (Amended) A pharmaceutical composition comprising:
- a. a therapeutically effective amount of a first compound, said first compound being

Cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro  
-naphthalene-2-ol;

(-)-Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-  
naphthalene-2-ol;

Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-  
naphthalene-2-ol;

Cis-1-[6'-pyrrolodinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-  
tetrahydrohaphthalene;

1-(4'-Pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-  
tetrahydroisoquinoline;

Cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-  
tetrahydro-naphthalene-2-ol; or

1-(4'-Pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-  
tetrahydroisoquinoline; and

- b. a therapeutically effective amount of a second compound, said second compound  
being sodium fluoride, a parathyroid hormone, or growth hormone.

Please cancel claim 51 without prejudice or disclaimer.

Please amend claim 52 as follows:

52. (Amended) A method for treating a mammal having a condition which presents with low bone mass comprising administering to a mammal having a condition which presents with low bone mass

a. a therapeutically effective amount of a first compound, said first compound being

Cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

(-)-Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

Cis-1-[6'-pyrrolidinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydro-naphthalene;

1-(4'-Pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

Cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; or

1-(4'-Pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline; and

- b. a therapeutically effective amount of a second compound, said second compound being sodium fluoride, a parathyroid hormone, or growth hormone.

Please cancel claims 56, 63, and 64 without prejudice or disclaimer.

Please amend claims 65 and 73 as follows:

65. (Amended) A kit containing a treatment for a condition which presents with low bone mass comprising:
- a. a therapeutically effective amount of
- Cis*-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;
- (-)-*Cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;
- Cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;
- Cis*-1-[6'-pyrrolidinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydrohaphthalene;
- 1-(4'-Pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;
- Cis*-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; or

1-(4'-Pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline  
and a pharmaceutically acceptable carrier in a first unit dosage form;

b. a therapeutically effective amount of sodium fluoride, a parathyroid hormone, or growth hormone and a pharmaceutically acceptable carrier in a second unit dosage form; and

c. container means for containing said first and second dosage forms.

73. (Amended) A pharmaceutical composition comprising:

a. a therapeutically effective amount of a first compound, said first compound being raloxifene, tamoxifen or idoxifene; and

b. a therapeutically effective amount of a second compound, said second compound being a parathyroid hormone or growth hormone.

Please cancel claim 78 without prejudice or disclaimer.

Please amend claim 79 as follows:

79. (Amended) A method for treating a mammal having a condition which presents with low bone mass comprising administering to a mammal having a condition which presents with low bone mass

a. a therapeutically effective amount of a first compound, said first compound being raloxifene, tamoxifen or idoxifene; and

b. a therapeutically effective amount of a second compound, said second compound

being a parathyroid hormone or growth hormone.

Please cancel claims 83, 90, and 91 without prejudice or disclaimer.

92. (Amended) A kit containing a treatment for a condition which presents with low bone mass comprising:

- a. a therapeutically effective amount of raloxifene, tamoxifen or idoxifene; and a pharmaceutically acceptable carrier in a first unit dosage form;
- b. a therapeutically effective amount of a parathyroid hormone or growth hormone and a pharmaceutically acceptable carrier in a second unit dosage form; and
- c. container means for containing said first and second dosage forms.

Please add new claims 93-108, as follows:

93. (New) A combination that comprises an estrogen agonist/antagonist and a growth hormone secretagogue.
94. (New) The combination of claim 93, wherein the growth hormone secretagogue is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide or its L-tartaric acid salt.
95. (New) The combination of claim 93, wherein the estrogen agonist/antagonist is raloxifene or a pharmaceutically acceptable salt thereof.
96. (New) The combination of claim 93, wherein the estrogen agonist/antagonist is (-)-Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or a pharmaceutically acceptable salt thereof.

97. (New) A method for treating a condition which presents with low bone mass comprising administering to a patient in need thereof a therapeutically effective amount of the combination of claim 93.
98. (New) A method for treating a condition which presents with low bone mass comprising administering to a patient in need thereof a therapeutically effective amount of the combination of claim 94.
99. (New) A method for treating a condition which presents with low bone mass comprising administering to a patient in need thereof a therapeutically effective amount of the combination of claim 95.
100. (New) A method for treating a condition which presents with low bone mass comprising administering to a patient in need thereof a therapeutically effective amount of the combination of claim 96.
101. (New) The method of claim 97 wherein the condition is osteoporosis.
102. (New) A pharmaceutical composition comprising an estrogen agonist/antagonist, a growth hormone secretagogue, and a pharmaceutically acceptable carrier.
103. (New) The composition of claim 102, wherein the growth hormone secretagogue is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide or its L-tartaric acid salt.
104. (New) The composition of claim 102, wherein the estrogen agonist/antagonist is raloxifene or a pharmaceutically acceptable salt thereof.



105. (New) The composition of claim 102, wherein the estrogen agonist/antagonist is (-)-Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol or a pharmaceutically acceptable salt thereof.
106. (New) A process for making a pharmaceutical composition comprising combining an estrogen agonist/antagonist, a growth hormone secretagogue, and a pharmaceutically acceptable carrier.
107. (New) The process of claim 106, wherein the estrogen agonist/antagonist is raloxifene, (-)-Cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)]-5,6,7,8-tetrahydro-naphthalene-2-ol or a pharmaceutically acceptable salt thereof.
108. (New) The process of claim 106, wherein the growth hormone secretagogue is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide or its L-tartaric acid salt.